

The AP-2 clathrin adaptor mediates endocytosis of an inhibitory killer cell Ig-like receptor in human NK cells

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Abstract

Copyright © 2014 by The American Association of Immunologists, Inc. All rights reserved. Stable surface expression of human inhibitory killer cell Ig-like receptors (KIRs) is critical for controlling NK cell function and maintaining NK cell tolerance toward normal MHC class I+ cells. Our recent experiments, however, have found that Ab-bound KIR3DL1 (3DL1) readily leaves the cell surface and undergoes endocytosis to early/recycling endosomes and subsequently to late endosomes. We found that 3DL1 internalization is at least partially mediated by an interaction between the μ 2 subunit of the AP-2 clathrin adaptor complex and ITIM tyrosine residues in the cytoplasmic domain of 3DL1. Disruption of the 3DL1/ μ 2 interaction, either by mutation of the ITIM tyrosines in 3DL1 or mutation of μ 2, significantly diminished endocytosis and increased surface expression of 3DL1 in human primary NK cells and cell lines. Furthermore, we found that the 3DL1/AP-2 interaction is diminished upon Ab engagement with the receptor, as compared with untreated cells. Thus, we have identified AP-2-mediated endocytosis as a mechanism regulating the surface levels of inhibitory KIRs through their ITIM domains. Based on our results, we propose a model in which nonengaged KIRs are internalized by this mechanism, whereas engagement with MHC class I ligand would diminish AP-2 binding, thereby prolonging stable receptor surface expression and promoting inhibitory function. Furthermore, this ITIM-mediated mechanism may similarly regulate the surface expression of other inhibitory immune receptors.

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